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ARTICLE

Effect of discontinuation of lemborexant following long-term treatment of insomnia disorder: Secondary analysis of a randomized clinical trial

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Abstract

Discontinuing long-term pharmacotherapy for insomnia can result in rebound insomnia or withdrawal symptoms and suboptimal treatment. Post hoc analyses evaluated rebound insomnia and withdrawal symptoms among the subset of subjects from a phase III, 12-month, global, multicenter, randomized, double-blind, parallel-group study who completed 12 or 6 months of active treatment and follow-up period. Study E2006-G000-303 (Study 303) included adults ($N = 655$) with subjective sleep-onset latency ≥30 min and/or subjective wake-after-sleep onset ≥60 min at least three times weekly during the 4 weeks before enrollment. Subjects were randomized 1:1:1 to lemborexant 5 mg (LEM5) or 10 mg (LEM10) or placebo for 6 months. Thereafter, for an additional 6 months, LEM5- and LEM10-treated subjects continued lemborexant and the placebo group was rerandomized 1:1 to LEM5 or LEM10. Month 12 was followed by abrupt discontinuation and a 2-week end-of-study follow-up. Using daily electronic sleep diaries, patients reported (subjective) sleep end points (sleep-onset latency, wake-after-sleep onset, sleep efficiency, and total sleep time). Withdrawal symptoms were assessed using the Tyrer Benzodiazepine Withdrawal Symptoms Questionnaire (T-BWSQ). Sleep outcome improvements with lemborexant at month 12 were generally maintained throughout the 2-week off-treatment period wherein <20% of subjects experienced significant worsening of insomnia symptoms versus screening. There was no evidence of withdrawal symptoms by T-BWSQ following lemborexant discontinuation. This analysis demonstrates rebound insomnia is unlikely to occur with lemborexant, and its effectiveness is maintained after abrupt discontinuation without placebo replacement following 6–12 months of treatment.

Yoshikazu Takaesu and Masahiro Suzuki contributed equally this work.

Trial registration: ClinicalTrials.gov, NCT02952820 and ClinicalTrialsRegister.eu, 2015-001463-39.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Discontinuation of some hypnotic drugs can result in rebound insomnia or withdrawal. Rebound insomnia, which is usually temporary, may involve worsening of the insomnia originally being treated.

WHAT QUESTION DID THIS STUDY ADDRESS?

These post hoc analyses evaluated effects of treatment discontinuation in 6- to 12-month lemborexant-treated subjects (lemborexant 5 or 10 mg daily), followed by a 2-week follow-up period with no placebo replacement so clinicians could more easily interpret the safety data of lemborexant after discontinuation. These analyses also assessed the potential influence of lemborexant dose/treatment duration on the rate of sleep parameter worsening, along with what potential new adverse events might have emerged.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This analysis demonstrates rebound insomnia is unlikely to occur with lemborexant, and its effectiveness is maintained after abrupt discontinuation following 6–12 months of treatment.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

These findings suggest patients with insomnia can be treated with lemborexant long term without the fear of potential adverse effects of withdrawal and rebound insomnia reported for other insomnia pharmacotherapies.

INTRODUCTION

Although many pharmacologic treatments for insomnia are approved for short-term use, patients may use them chronically.[1] Unfortunately, discontinuation of some hypnotic drugs can result in rebound insomnia or withdrawal.[2] Rebound insomnia, which is usually temporary and may involve worsening of the insomnia for which the drug was originally prescribed,[3] can heighten an individual's anxiety and resistance to discontinuing hypnotics.[4] Studies have shown that withdrawal symptoms from benzodiazepines can lead to life-threatening seizures[5] in addition to other symptoms, including increased irritability and tension, anxiety, panic attacks, hand tremors, sweating, nausea, headaches, and muscle pain.[6] Therefore, it is important to address the potential for rebound insomnia and withdrawal symptoms when discontinuing insomnia treatment.

Lemborexant is an orally active, dual orexin receptor antagonist (DORA) approved in several countries, including the Unites States, Japan, Canada, Australia, and several Asian countries, for the treatment of insomnia in adults. Lemborexant has demonstrated significant clinical benefit in the treatment of insomnia across phase II and III clinical trials.[7–10] As their mechanism of action differs from other classes of insomnia medication,[11] DORAs may have less potential for addiction and, subsequently, less incidence of rebound insomnia.[11]

In the phase III randomized clinical trial study E2006-G000-303 (Study 303; SUNRISE-2; ClinicalTrials.gov, NCT02952820; ClinicalTrialsRegister.eu, 2015-001463-39),[7] adults with insomnia were treated with lemborexant for up to 12 months, followed by abrupt discontinuation and a 2-week follow-up period. No evidence of rebound insomnia was found in the overall treatment population of Study 303 who received either a 5 mg (LEM5) or 10 mg (LEM10) daily dose of lemborexant from initial randomization.[10] However, a portion of patients in the full analysis set (221 of 971 [22.8%] randomized to active treatment) discontinued the allocated treatment at month 6 or earlier. Additionally, rebound insomnia was defined as having a subjective sleep onset latency (sSOL) and subjective wake after sleep onset (sWASO) more than 5 min longer than during screening, which is difficult to interpret in clinical practice.

Given these caveats, the current post hoc analyses of Study 303 aimed to further explore the potential effects of lemborexant treatment discontinuation in subsets of patients who completed either 6 or 12 months of active treatment with LEM5 or LEM10 daily. Effects of discontinuation were evaluated during a 2-week follow-up period with no placebo replacement, which allows clinicians to interpret

the safety data of lemborexant after discontinuation more easily. The lack of placebo replacement is consistent with the expectation that patients would be aware of a treatment discontinuation in real-world situations. The current study also explores the influence of lemborexant dose and treatment duration on the rate of sleep parameter worsening, along with the potential emergence of new adverse events (AEs) upon abrupt discontinuation that would be suggestive of rebound insomnia and/or withdrawal.

METHODS

Study design

Study 303 was a 12-month, global, multicenter, randomized, placebo-controlled (first 6 months), double-blind, parallel-group phase III study (Figure S1). Details of the methodology and study population have been published previously.[7,10] Briefly, men and women aged ≥18 years (range: 18–88 years) with insomnia disorder were required to have a history of sSOL ≥30 min and/or sWASO ≥60 min at least three times weekly during the 4 weeks before enrollment. Eligible subjects completed an electronic sleep diary within 1 h of awakening each day throughout the study, including the 2 weeks following the final dose of study drug (follow-up period).

Following a 2-week placebo run-in period, subjects were randomized 1:1:1 to once-daily placebo, LEM5, or LEM10. After 6 months, all subjects assigned to the placebo group were rerandomized (1:1) to LEM5 or LEM10; those assigned to lemborexant at the start of the study continued with the same dose for an additional 6 months. Therefore, subjects initially randomized to LEM5 or LEM10 received the same dose for 12 continuous months (LEM5-LEM5 and LEM10-LEM10) and those rerandomized from placebo received LEM5 or LEM10 (PBO-LEM5 and PBO-LEM10, respectively) for 6 months following rerandomization.

During the 2-week follow-up period (after the final dose of lemborexant), no study drugs, including placebo, were administered and subjects continued to complete their daily sleep diaries until the end-of-study visit. Study 303 was designed to have a 2-week follow-up period based on the results from the previous phase II trial.[8] Although it is noteworthy that some lemborexant is present in plasma after 2 days of withdrawal (based on the half-life), Murphy et al.[8] reported no evidence for rebound insomnia in sleep diary data from the 2 weeks post-treatment and the polysomnography data for the 2 days after discontinuation of lemborexant. A 2-week follow-up period is in a similar range of other phase III studies of sleep-promoting drugs.[12]

Study 303 adhered to the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulations. The study protocol and amendments were approved by the appropriate institutional review boards and independent ethics committees. All study participants provided informed consent prior to screening.[7] A Consolidated Standards of Reporting Trials (CONSORT) flow chart for this study is presented in Figure S2.

Analysis population

Subjects who completed the study were included in the 6-month active completers analysis set (placebo [PBO]-LEM5 and PBO-LEM10 groups) and 12-month active completers analysis set (LEM5-LEM5 and LEM10-LEM10 groups). "Active" refers to any subject treated with LEM5 or LEM10. The following subgroups within the active completers analysis sets were defined as follows:

- Latency complainers: subjects with a mean sSOL >30 min during the screening period (last seven nights before placebo run-in).
- Maintenance complainers: subjects with a mean sWASO >60 min during the screening period.

Subjects with both latency and maintenance complaints were included in both subgroups.

Efficacy assessments

Sleep end points were calculated from the subjects' electronic sleep diaries. The sSOL was defined as the estimated time in minutes from the initial sleep attempt to sleep onset. The sWASO was defined as the sum of estimated minutes of wake during the night after initial sleep onset, until the subject got out of bed for the day. Subjective total sleep time (sTST) was derived from the total minutes spent asleep in bed. Subjective sleep efficiency (sSE) was expressed as the proportion of sTST per subjective time in bed.

The latency complainer and maintenance complainer subgroups were assessed for worsening of sSOL and sWASO from screening to the follow-up period. A worsening of sSOL or sWASO was defined as an increase of >0 min from the screening period (prior to the placebo run-in period). In addition to analyses in the overall 6- and 12-month active completers analysis sets, separate analyses were conducted to assess the proportion of latency complainers or maintenance complainers with worsening sSOL or sWASO during the follow-up period compared with screening. Defining subjects as latency complainers or maintenance complainers allows a similar analysis as performed in trials of suvorexant, another drug in the DORA class.[13,14]

Safety assessments

Safety was monitored in all subjects who received at least one dose of study drug and had at least one postdose safety assessment, as previously described.[7,10] Data from the follow-up period for subjects in the 6- and 12-month active completers analysis sets are reported here.

At the end-of-study visit (follow-up), the Tyrer Benzodiazepine Withdrawal Symptoms Questionnaire (T-BWSQ)[15] was used to assess the presence or absence of 20 possible withdrawal symptoms (no = 0; yes-moderate = 1; and yes-severe = 2). Responses sum to a maximum score of 40, with higher scores estimating higher withdrawal severity. Mean scores and the proportion of subjects reporting a T-BWSQ score ≥3 was calculated.

Statistical analyses

Statistical analyses were performed using SAS version 9.4 (SAS Institute) or other validated software by Eisai or a designee.

Analysis methods for sleep onset and maintenance outcomes in Study 303 have been previously reported.[7,10] For the assessments of temporal sleep parameters changes through the follow-up period, descriptive analyses are presented because there was no placebo comparator; therefore, formal statistical analyses were not possible.

For each sleep parameter, 95% confidence intervals (CIs) were compared for the least squares (LS) mean value for month 12 versus the LS mean value for the follow-up period. The LS mean and CIs were calculated using analysis of covariance, with treatment group, region, and age group as fixed effects.

Proportions of subjects who experienced worsening of sSOL and sWASO from screening during follow-up were calculated using data from the first night, averaged data from nights 1–7 and averaged data from nights 1–14. Logistic regression analysis was used to evaluate the extent that doses and duration of treatment could impact the rate of worsening sSOL and/or sWASO; corresponding screening values were used as covariates.

RESULTS

Disposition and baseline characteristics

The 12-month active completers analysis set included 226 and 203 subjects in the LEM5-LEM5 and LEM10-LEM10 groups, respectively (Table S1). The 6-month active completers analysis set included 116 and 110 subjects in the PBO-LEM5 and PBO-LEM10 groups, respectively. Similar to the overall study population reported elsewhere,[7] subjects in this analysis were 18–83 years of age (median 56–58 years across treatment groups) and predominately female subjects (64%–70% across treatment groups). Subject demographics and baseline characteristics were similar between treatment groups (Table S1). However, subjects in the LEM10-LEM10 group reported numerically greater sSOL (median) at baseline, and greater sWASO and lower sSE and sTST at screening, compared with subjects in the other three treatment groups (i.e., LEM5-LEM5, PBO-LEM5, and PBO-LEM10).

Temporal changes in sleep outcome

Sleep outcome improvements with lemborexant at month 12 were generally maintained in the 2-week follow-up period (Figure 1; Figure S3). The sustained improvements were similar between LEM5 and LEM10, as well as similar between 6- and 12-month LEM treatment durations.

Except for sSOL in the LEM5-LEM5 group, other sleep outcomes in each treatment group were not remarkably different during the 2-week follow-up compared with month 12, as evidenced by overlapping 95% CIs between these timepoints (Figure 2; Figure S4).

Despite small numerical increases in sSOL and sWASO during the 2-week follow-up compared with month 12, LS mean values remained much lower (improved) than those observed at screening (Figure 2). Similarly, although mean sSE was numerically lower during follow-up compared with month 12, sSE remained improved during the follow-up period compared with screening (Figure S4).

Incidence of worsening insomnia during follow-up

The proportions of latency complainers and maintenance complainers whose sSOL and/or sWASO worsened (where sSOL/sWASO was higher for the first night, the average of the first 7 nights and the average of the 14 days of follow-up vs. screening) upon lemborexant discontinuation were examined. The majority (83.7%) of latency complainers did not experience worsening of sSOL in the follow-up period relative to screening (Figure 3; Table S2). Similarly, most (84.1%) maintenance complainers did not experience worsening of sWASO in the follow-up period relative to screening (Table S2).

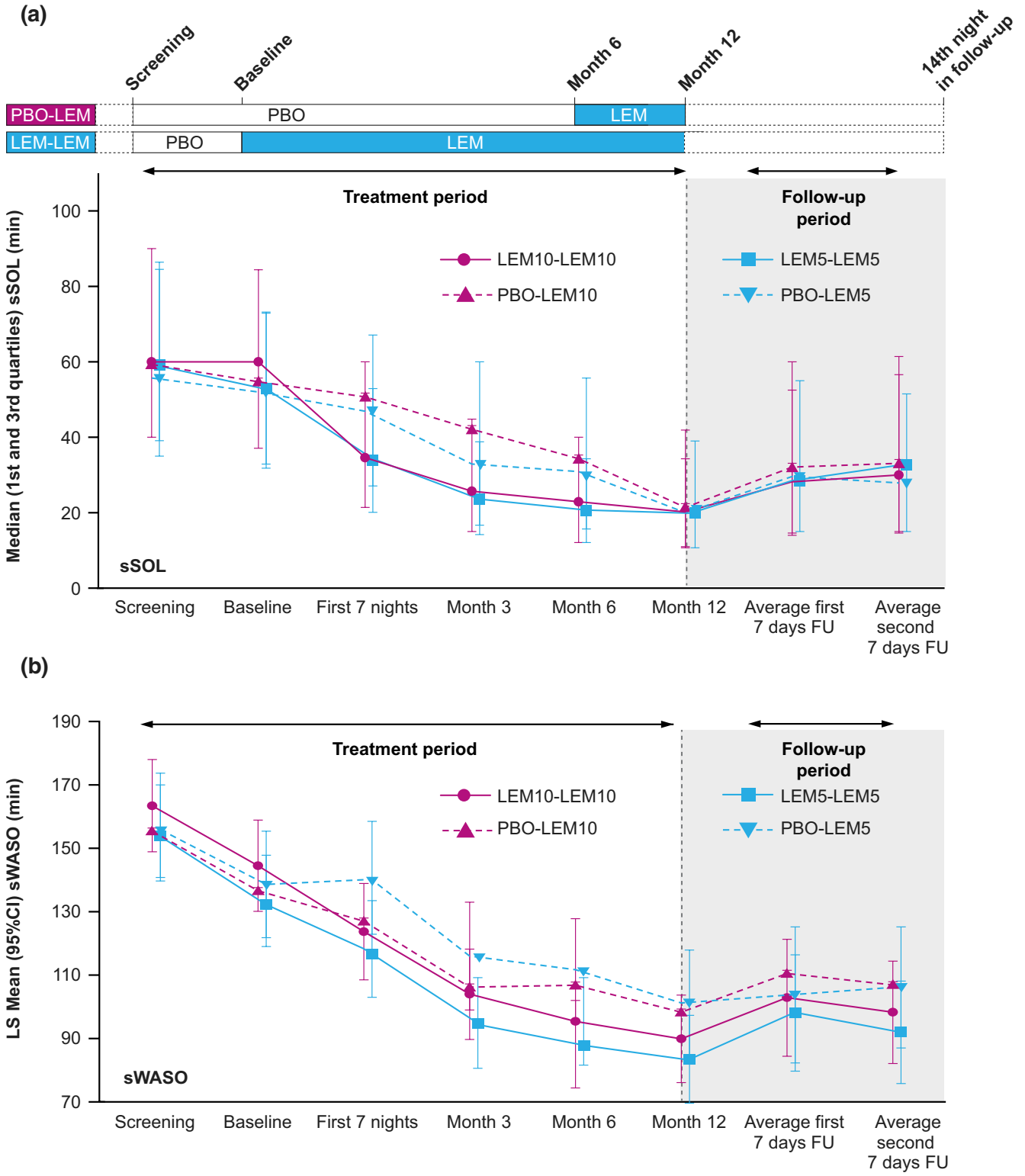


FIGURE 1 Change in (a) sSOL and (b) sWASO. Treatment period and during follow-up (weekly average) in subjects who completed 6 or 12 months of LEM5 or LEM10 (6- and 12-month active completers analysis sets). Subjects in the PBO-LEM5 and PBO-LEM10 groups received lemborexant during months 6–12; the month 12 timepoint reflects lemborexant treatment effects for these groups. Error bars indicate the (a) interquartile ranges or (b) 95% CI. Findings by day during the follow-up period for sSOL and sWASO as well as for sSE and sTST are presented in Figure S3. CI, confidence interval; FU, follow-up; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; LS, least squares; PBO, placebo; sSE, subject sleep efficiency; sSOL, subjective sleep onset latency; sTST, subjective total sleep time; sWASO, subjective wake after sleep onset.

Characteristics of subjects with worsening insomnia

The proportion of subjects experiencing worsening of insomnia symptoms was small (<20%). In regression analyses, maintenance complainers who took LEM10 for 12 months had a lower risk of worse sWASO than those who took LEM10 for 6 months ($p = 0.0045$; odds ratio 0.390; 95% CI, 0.203–0.747; Table 1). However, it should be noted that baseline and screening values for sWASO are not comparable across these groups; hence, firm conclusions cannot be drawn.

Effect of treatment discontinuation on safety

Among subjects completing 12 months of treatment, AEs occurred in 7.1% ($n = 16/226$) of subjects in the LEM5-LEM5 group and 5.4% ($n = 11/203$) of subjects in the LEM10-LEM10 group during the 2-week follow-up period after treatment discontinuation (Table 2). Among subjects who completed 6 months of treatment, AEs were reported in 11.2% ($n = 13/116$) of subjects in the PBO-LEM5 group and 6.7% ($n = 7/110$) of the PBO-LEM10 group during the 2-week follow-up period. All AEs were mild to moderate in severity.

No new AEs suggestive of rebound were observed following discontinuation of lemborexant (Table 2). One subject reported the return of insomnia on day 11 of the follow-up period; however, it resolved the following day.

Withdrawal symptoms following treatment discontinuation

Among 12-month active treatment completers, the mean (SD) T-BWSQ score was 1.42 (2.49) and 1.10 (2.34) among subjects in the LEM5-LEM5 and LEM10-LEM10 groups, respectively, with similar scores observed among 6-month active completers (Table 3).

Few (<18.5% in any group) 12-month and 6-month active completers had T-BWSQ scores ≥3 (Table 3). These findings suggest no evidence of withdrawal symptoms following lemborexant discontinuation; there were no apparent differences based on lemborexant treatment dose and duration.

DISCUSSION

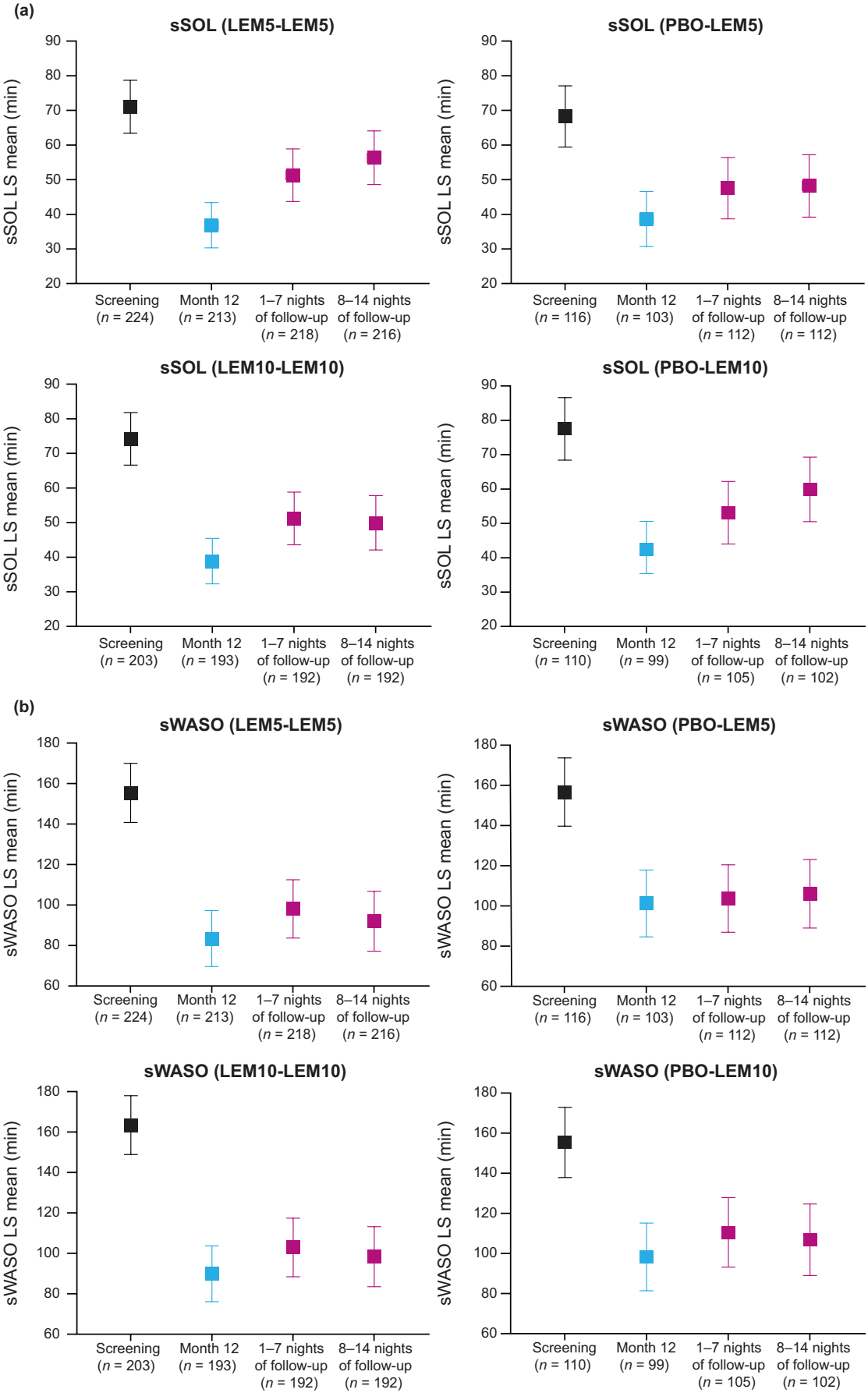
This post hoc analysis of Study 303 demonstrates that rebound insomnia is unlikely following abrupt discontinuation of 6–12 months of lemborexant treatment. Moreover, sleep outcomes during the follow-up period were similar to those achieved at month 12 of lemborexant treatment, with no return of pretreatment (screening) levels, suggesting that the improvements observed with active treatment can be maintained after lemborexant is discontinued. The safety profile was similar to that previously reported in Study 303, with <10% of subjects experiencing AEs following lemborexant discontinuation.[10]

Overall, fewer than 20% of treatment completers experienced worsening of insomnia after lemborexant discontinuation in this analysis. Of note, relapses can occur after partial remission as part of the natural history of insomnia.[16] Considering that rebound insomnia usually occurs within a few days after treatment discontinuation, and that the worsening of insomnia after withdrawal of lemborexant was stable throughout the 14-day follow-up period, it is likely that some of the cases of insomnia worsening observed in this study reflect the recurrence of insomnia symptoms after remission.

Discontinuation of some insomnia treatments poses challenges to drug management. For example, benzodiazepine use may cause physical dependence and tolerance.[17] One study of subjects with chronic insomnia found that their subjective sleep latency after withdrawal of 7-day treatment of 30 mg midazolam increased to 103.9 min compared to 46.7 min on baseline ($p < 0.01$).[18] The lack of a gold standard approach to discontinuing hypnotics is also a challenge to prescribing pharmacology treatment, as the tapering method can be troublesome and time-consuming for some clinicians.[17]

Rebound insomnia has also been evaluated following discontinuation of other DORAs. For example, no strong evidence of rebound insomnia has been observed with suvorexant in clinical trials of varying duration.[12–14,19] Michelson et al. reported that after 12 months of suvorexant 40 mg (30 mg for elderly subjects), 33.8% ($n = 48/142$) had worse sSOL on the first night of the placebo run-out period compared with month 0 baseline; there were no significant differences between the suvorexant and placebo groups during run-out.[14] The effect of treatment discontinuation of the DORA daridorexant was assessed in phase

FIGURE 2 Comparison of 95% CI for (a) sSOL and (b) sWASO. Month 12 and during follow-up in subjects who completed 6 or 12 months of LEM5 or LEM10 (6- and 12-month active completers analysis sets). Error bars represent 95% CI. Differences between timepoints were assumed to be nonsignificant if 95% CIs overlapped. Similar findings for sSE and sTST are presented in Figure S4. CI, confidence interval; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; LS, least squares; PBO, placebo; sSE, subject sleep efficiency; sSOL, subjective sleep onset latency; sTST, subjective total sleep time; sWASO, subjective wake after sleep onset.


(a)
sSOL (LEM5-LEM5)
sSOL (PBO-LEM5)
sSOL (LEM10-LEM10)
sSOL (PBO-LEM10)
sSOL LS mean (min)
90
80
70
60
50
40
30
20
Screening (n = 224)
Month 12 (n = 213)
1–7 nights of follow-up (n = 218)
8–14 nights of follow-up (n = 216)
Screening (n = 116)
Month 12 (n = 103)
1–7 nights of follow-up (n = 112)
8–14 nights of follow-up (n = 112)
Screening (n = 203)
Month 12 (n = 193)
1–7 nights of follow-up (n = 192)
8–14 nights of follow-up (n = 192)
Screening (n = 110)
Month 12 (n = 99)
1–7 nights of follow-up (n = 105)
8–14 nights of follow-up (n = 102)
(b)
sWASO (LEM5-LEM5)
sWASO (PBO-LEM5)
sWASO (LEM10-LEM10)
sWASO (PBO-LEM10)
sWASO LS mean (min)
180
160
140
120
100
80
60
Screening (n = 224)
Month 12 (n = 213)
1–7 nights of follow-up (n = 218)
8–14 nights of follow-up (n = 216)
Screening (n = 116)
Month 12 (n = 103)
1–7 nights of follow-up (n = 112)
8–14 nights of follow-up (n = 112)
Screening (n = 203)
Month 12 (n = 193)
1–7 nights of follow-up (n = 192)
8–14 nights of follow-up (n = 192)
Screening (n = 110)
Month 12 (n = 99)
1–7 nights of follow-up (n = 105)
8–14 nights of follow-up (n = 102)

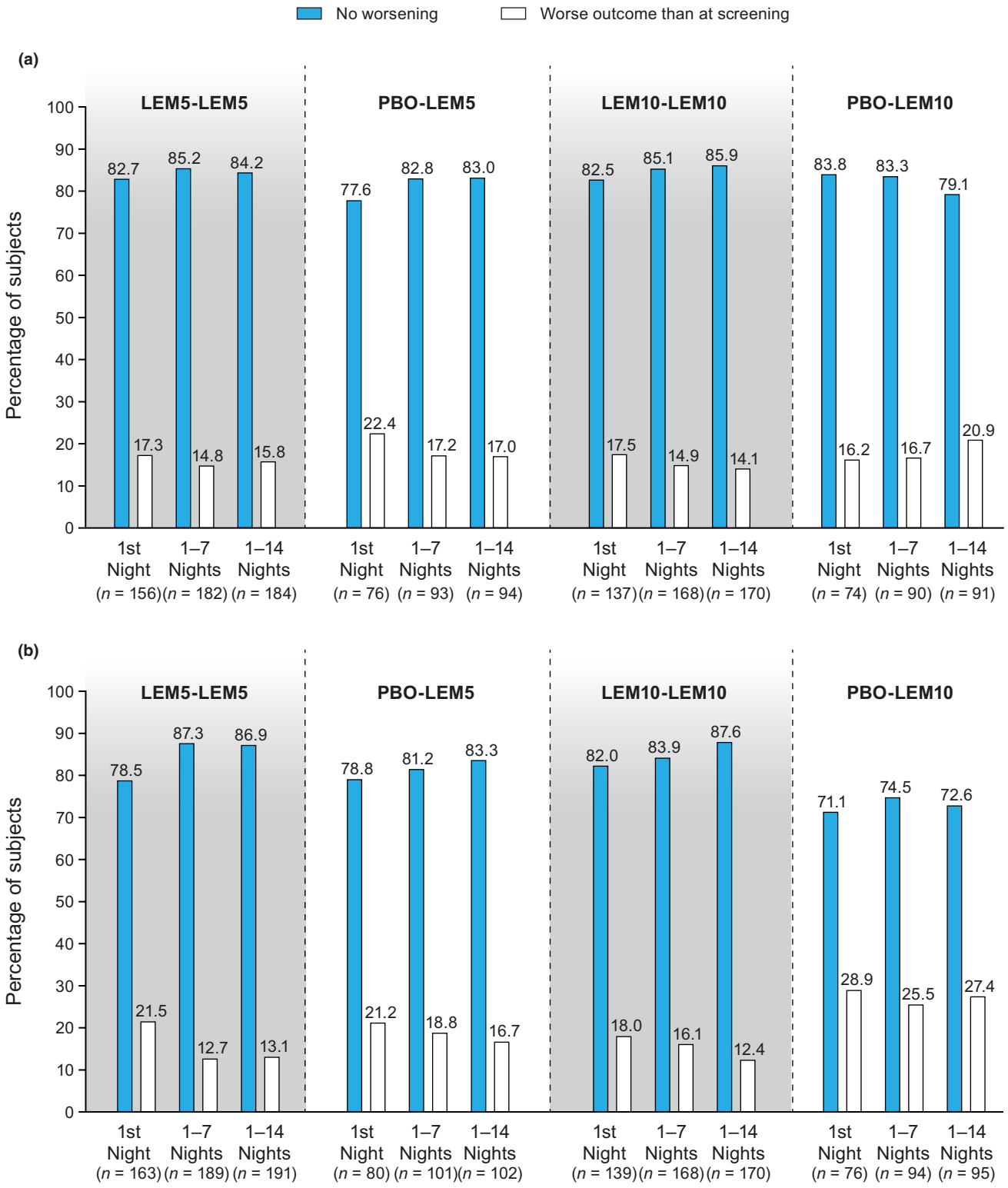


FIGURE 3 Subjects experiencing worsening since screening.[a] (a) sSOL and (b) sWASO during the 2-week follow-up period, among the subgroups of latency complainers[b] and maintenance complainers,[c] respectively. [a]Defined as an increase >0 min from the screening period. [b]Defined as subjects who had a mean sSOL >30 min during the screening period. [c]Defined as subjects who had a mean sWASO >60 min during the screening period. LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; PBO, placebo; sSOL, subjective sleep onset latency; sWASO, subjective wake after sleep onset.

III clinical trials, which included 3 months of treatment followed by a 7-day placebo run-out period.[20] Patients administered daridorexant 50 or 25 mg experienced mean decreases in sTST during the placebo run-out period relative to the last on-treatment assessment.[20] However, values during the run-out remained numerically higher in sTST

TABLE 1 Logistic regression analysis on predictors of worsening at follow-up (mean over 14 days) compared with screening

	Explanatory variable	Adjusted OR	95% CI	*p* value
Latency complainers[a]—sSOL worsening				
Dose of 12-month treatment (10 mg vs. 5 mg)	LEM10-LEM10 vs. LEM5-LEM5	0.892	0.485–1.606	0.7024
Dose of 6-month treatment (10 mg vs. 5 mg)	PBO-LEM10 vs. PBO-LEM5	1.348	0.640–2.839	0.4316
Duration of 5-mg treatment (12 vs. 6 months)	LEM5-LEM5 vs. PBO-LEM5	0.927	0.472–1.821	0.8250
Duration of 10-mg treatment (12 vs. 6 months)	LEM10-LEM10 vs. PBO-LEM10	0.612	0.314–1.193	0.1495
Maintenance complainers[b]—sWASO worsening				
Dose of 12-month treatment (10 mg vs. 5 mg)	LEM10-LEM10 vs. LEM5-LEM5	0.952	0.511–1.775	0.8778
Dose of 6-month treatment (10 mg vs. 5 mg)	PBO-LEM10 vs. PBO-LEM5	1.908	0.952–3.824	0.0686
Duration of 5-mg treatment (12 vs. 6 months)	LEM5-LEM5 vs. PBO-LEM5	0.753	0.386–1.471	0.4067
Duration of 10-mg treatment (12 vs. 6 months)	LEM10-LEM10 vs. PBO-LEM10	0.390	0.203–0.747	0.0045

Note: Screening values were used as a covariate.

Abbreviations: CI, confidence interval; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; OR, odds ratio; PBO, placebo; sSOL, subjective sleep onset latency; sWASO, subjective wake after sleep onset.

[a]Defined as subjects with a mean sWASO >60 min during the screening period.

[b]Defined as subjects with a mean sSOL >30 min during the screening period.

TABLE 2 Summary of number of AEs during the 2-week follow-up period in subjects who completed 6 or 12 months of LEM5 or LEM10 therapy (6- and 12-month active completers analysis sets)

AEs, *n*	LEM5-LEM5 (*n* = 226)	PBO-LEM5 (*n* = 116)	LEM10-LEM10 (*n* = 203)	PBO-LEM10 (*n* = 110)
Total AEs	18	15	14	7
Subjects experiencing an AE	16	13	11	7
Severity				
Mild	13	11	4	3
Moderate	5	4	10	4
Severe	0	0	0	0
AEs occurring in >1 subject overall				
Headache	0	3	1	0
AST increased	0	2	1	0
Upper respiratory tract infection	2	0	0	1
Urinary tract infection	0	0	2	1
ALT increased	0	1	1	0
Cystitis	0	0	1	1
Nasopharyngitis	1	0	1	0
Pharyngitis	0	1	1	0

Note: Some subjects had multiple AEs, including multiple AEs of the same description.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; PBO, placebo.

TABLE 3 Withdrawal symptoms following lemborexant discontinuation among 12-month and 6-month active treatment completers, based on the T-BWSQ

	LEM5-LEM5 ($n = 223$)	PBO-LEM5 ($n = 115$)	LEM10-LEM10 ($n = 202$)	PBO-LEM10 ($n = 108$)
T-BWSQ				
Mean (SD)	1.42 (2.49)	1.41 (2.51)	1.10 (2.34)	1.28 (2.51)
T-BWSQ ≥3				
n (%)	41 (18.4%)	21 (18.3%)	28 (13.9%)	18 (16.7%)

Abbreviations: LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; PBO, placebo; SD, standard deviation; T-BWSQ, Tyrer Benzodiazepine Withdrawal Symptoms Questionnaire.

than the respective baseline values and, thus, were not considered evidence of rebound insomnia.[21] Moreover, studies of the melatonin receptor agonist ramelteon found no evidence of rebound insomnia defined based on various patient-reported assessments following treatment durations ranging from 5 to 24 weeks.[22,23] Twelve- and 24-week studies of eszopiclone have also reported no occurrence of rebound insomnia (based on patient-reported sleep assessments) in adults with primary and comorbid insomnia.[24,25] In addition, the non-benzodiazepine hypnotics zaleplon and zolpidem have not been found in most studies to be associated with rebound insomnia following discontinuation. Evidence exists, however, that zolpidem may cause rebound insomnia based on subjective assessment on the first night following discontinuation after 3 to 4 weeks of treatment.[1,26]

In the present study, there was no placebo run-out for rebound insomnia evaluation, which allows clinicians to interpret the safety data of lemborexant after discontinuation more easily, whereas it may be difficult to assess pharmacological effects of the drug (i.e., physical dependence) separately from expectation the subjects may feel by knowing their treatment is discontinued abruptly. Therefore, there should be caution in interpreting the results of the current analysis when juxtaposing with the study results of other hypnotics.

In addition, there was a difference in recruitment criteria of the subjects in the abovementioned reports. For example, in clinical trials of suvorexant, ramelteon, and eszopiclone, subjects were included on the basis of subjective sleep latency and sTST[13,14,23,25] criteria; subjective latency, sTST, and sWASO in the daridorexant trial[21]; subjective latency and either sTST or nocturnal awakenings in the zaleplon trial[26]; and sTST and sWASO in one of the eszopiclone trials.[24] Meanwhile, in Study 303, subjects were recruited according to sSOL and/or sWASO criteria, likewise in the midazolam study,[18] which may include patients with a wider profile range. Therefore, in the present analysis, we defined latency complainer and maintenance complainer and analyzed them separately. Most subjects (>70%) within each category did not experience worsening of their chief sleep complaint(s). Regression analyses of characteristics of the small number of latency complainers and maintenance complainers experiencing rebound do not suggest a clear contribution of lemborexant dose or treatment duration to rate of worsening of sleep parameters. This tendency differs from that of benzodiazepine drugs, for which longer duration and higher dose are considered as risk factors for drug dependence.[5] For latency complainers and maintenance complainers, LEM10 versus LEM5 did not significantly affect the risk of sSOL or sWASO worsening, respectively, over 6 or 12 months. For sSOL, rebound was not significantly dependent on length of treatment for either dose of lemborexant. Subjects receiving LEM5 were not significantly more likely to experience rebound on sWASO based on length of treatment (6–12 months). Meanwhile, subjects who received LEM10 for 6 months showed a higher rate of worsening in sWASO compared with those who received LEM10 for 12 months. However, there was a disparity in the mean sWASO screening values for the 6-month LEM10 rebound group (mean sWASO: 130 min) when comparing the subjects in the LEM10 "rebound" group (154 min) and LEM10 "no rebound" group (174 min), which may help explain this difference.

Strengths and limitations

This analysis has certain methodological differences with other previous reports. Unlike many benzodiazepine studies,[17] subjects in Study 303 were aware they were discontinuing lemborexant. Moreover, in contrast to many previously described suvorexant, ramelteon, and daridorexant studies,[12–14,20–23] there was no drug or placebo substitution during the run-out. The lack of blinding and placebo replacement during the post-discontinuation follow-up period in this clinical trial study design hinders the present analysis from being discussed comparatively with other analyses with placebo run-out. On the other hand, this methodological difference is expected to approximate the typical patient experience more closely, as patients

would be aware they were discontinuing a pharmacotherapy. In addition, as no tapering was involved in this study, our findings suggest patients taking lemborexant may have the potential to easily discontinue without dose adjustment and rebound insomnia.

The current analysis of lemborexant discontinuation among 6- and 12-month treatment completers was post hoc in nature, and, as such, results should be interpreted with caution. Placebo recipients were switched to active (lemborexant) treatment after 6 months in Study 303, preventing analysis of lemborexant discontinuation effects in the context of a placebo discontinuation group. In addition, there are cons of placebo run-out for rebound insomnia evaluation, as it makes it difficult to assess the pharmacological effect of lemborexant (i.e., physical dependence) separately from the expectation the subjects may feel by knowing their treatment is discontinued abruptly. The study is also limited by the relatively short follow-up period for assessment of post-discontinuation insomnia variables (2 weeks). Whereas rebound insomnia usually occurs within a few days after treatment discontinuation, it is not possible to rule out the possibility of insomnia symptom rebound over the longer term. Moreover, a limitation of Study 303 is that subjects assigned to lemborexant might have received suboptimal doses leading to insufficient amelioration of insomnia symptoms throughout the study, as reported in a network meta-analysis that LEM10 outperformed LEM5 regarding sTST and sWASO at week 1 and month 1.[27] Additionally, the 6-month placebo treatment period that occurred before active treatment in the PBO-LEM5 and PBO-LEM10 groups might not represent real-world responses after 6 months of treatment, as such, 6-month placebo periods do not occur in clinical practice.

CONCLUSIONS

This post hoc analysis from a phase III study of lemborexant for insomnia disorder suggests that rebound insomnia is unlikely to occur after abrupt discontinuation of long-term treatment. Efficacy was maintained upon discontinuation and no new safety issues, including withdrawal symptoms, were observed, further supporting a lack of rebound insomnia with lemborexant discontinuation.

AUTHOR CONTRIBUTIONS

Y.T., M.S., M.M., K.P., K.I., Y.N., and K.K. wrote the manuscript. Y.T., M.S., M.M., K.I., Y.N., and K.K. designed the research. Y.T., M.S., M.M., K.P., K.I., Y.N., and K.K. performed the research. K.P. analyzed the data.

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CONFLICTS OF INTEREST

Y.T. has received grants or contracts from Otsuka Pharmaceutical, Meiji Seika Pharma, and MSD; and payment or honoraria from Eisai, Sumitomo Dainippon Pharma, Takeda Pharmaceutical, Otsuka Pharmaceutical, Meiji Seika Pharma, Kyowa Pharmaceutical, MSD, and Yoshitomi. M.S. has received grants or contracts from Novartis, Shionogi Pharma, Dainippon Sumitomo, Eisai, Mochida Pharmaceutical, Otsuka Pharmaceutical, Takeda Pharmaceutical; and payment or honoraria from Dainippon Sumitomo, Eisai, Mochida Pharmaceutical, Takeda Pharmaceutical, EA Pharma, Meiji Seika Pharma, MSD, Pfizer, Yoshitomi, Pharmaceutical, and Viatris. M.M. is an employee of Eisai Inc., Nutley, NJ, USA. K.P. is an employee of Eisai Ltd., Hatfield, UK. K.I. and Y.N. are employees of Eisai Co., Ltd., Bunkyo-ku, Tokyo, Japan. K.K. has received grants or contracts from Eisai, Otsuka Pharmaceutical, MSD, Sumitomo Pharma, Tsumura, Kao Corporation, Takeda Pharmaceutical, Shionogi Pharma, Pfizer, Yoshitomi Pharmaceutical, PMC Corporation; consulting fees from the municipal government office of Kodaira, Tokyo, Igakyu-Shoin; and payment or honoraria from Eisai, MSD, Takeda Pharmaceutical, Kao Corporation, Tsumura, Sumitomo Dainippon Pharma, and Yoshitomi Pharmaceutical.

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SUPPORTING INFORMATION

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